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Abstract

Background: Cadmium is a toxic metal classified as a human carcinogen by the International Agency for Research on Cancer.

Objective: To evaluate the association of long-term cadmium exposure, as measured in urine, with cancer mortality in American Indians from Arizona, Oklahoma and North/South Dakota who participated in the Strong Heart Study in 1989-91.

Methods: Prospective cohort study of 3,792 men and women 45-74 years of age who were followed for up to 20 years. Baseline urine cadmium was measured using inductively coupled plasma mass spectrometry. We assessed cancer events by annual mortality surveillance.

Results: Median (interquintile range) urine cadmium concentration was 0.93 (0.55, 1.63) μg/g creatinine. After adjustment for sex, age, smoking status, cigarette pack-years, and body mass index, adjusted hazard ratios comparing the 80th versus 20th percentiles of urine cadmium were 1.30 (95% CI: 1.09, 1.55) for total cancer, 2.27 (95% CI: 1.58, 3.27) for lung cancer, and 2.40 (95% CI: 1.39, 4.17) for pancreas cancer mortality. For all smoking-related cancers combined, the corresponding hazard ratio was 1.56 (95% CI: 1.24, 1.96). Cadmium was not significantly associated with liver, esophagus and stomach, colon and rectum, breast, prostate, kidney, or lymphatic and hematopoietic cancer mortality. Based on mediation analysis, we estimated the percentage of lung cancer deaths due to tobacco smoking that could be attributed to cadmium exposure was 9.0% (95%CI: 2.8, 21.8%).

Conclusions: Low to moderate cadmium exposure was prospectively associated with total cancer mortality and with mortality from cancers of the lung and pancreas. The implementation of population-based preventive measures to decrease cadmium exposure could contribute to reducing the burden of cancer.

Introduction

Cadmium is a widespread metal highly toxic to humans. Cadmium pollution in soil, air and water is ubiquitous due to cadmium use in industrial products (batteries, coatings and plastic stabilizers), contamination of phosphate fertilizers, and release from motor vehicle fuel combustion and tire wear (ATSDR 2011). Soil contamination is a major health problem because leafy/root vegetables and grains bio-concentrate cadmium, resulting in major sources of cadmium exposure through diet and smoking.

Cadmium was classified as a human carcinogen by the International Agency for Research on Cancer (IARC 1993). Cadmium exposure has been associated with lung cancer incidence in a population living in a cadmium polluted area (Nawrot et al. 2006) and with lung cancer incidence and mortality in occupationally exposed populations (Jarup et al. 1998; Park et al. 2012). In experimental models, cadmium acts as an endocrine disruptor (Martin et al. 2002; Siewit et al. 2010), supporting that this metal could potentially induce the development of hormone-dependent tumors in humans, such as those of the breast, uterus, and prostate (Akesson et al. 2008; Benbrahim-Tallaa et al. 2009; Bertin and Averbeck 2006). In occupationally exposed women, cadmium has been associated with breast cancer incidence (Pollán and Gustavsson 1999) and breast cancer mortality (Cantor et al. 1995). In other studies, however, occupational cadmium exposure was not associated with breast cancer incidence or mortality (Jarup et al. 1998, Kauppinen 2003). Some evidence also suggests that occupational cadmium exposure may be a risk factor for kidney (Il'yasova and Schwartz 2005) and pancreatic cancer (Schwartz and Reis 2000).

Less is known about the carcinogenicity of cadmium at low-moderate levels of exposure. In the Third National Health and Nutrition Examination Survey (1988-1994), urine cadmium was associated with total cancer mortality over 13.5 years of follow-up (Adams et al. 2012). In men, cadmium was associated with cancers of the lung and pancreas, and with non-Hodgkin lymphoma, but not with prostate cancer, while in women cadmium was associated with cancers of the lung, ovaries, and uterus, and with leukemia, but not with breast cancer (Adams et al. 2012). Cadmium exposure, however, has been associated with breast cancer in women from general populations in Sweden (Julin et al. 2012a) and the US (Gallagher et al. 2010; McElroy et al. 2006) and with cancer of the endometrium (Akesson et al. 2008.).

Cancer is the second leading cause of death in American Indians (CDC 2009). During 1999-2008, cancer death rates declined by more than 1% per year in every American ethnic/racial group with the exception of American Indians (Siegel et al. 2012). Few studies, however, have evaluated the cancer burden and its determinants in this population. The main objective of the present study was to evaluate the association of urine cadmium concentrations with overall and site-specific cancer mortality in American Indian adults who participated in the Strong Heart Study (SHS) in 1989-91 and were followed through 2008. In our study we assume that urine cadmium is a biomarker of long-term cadmium exposure (Jarup and Akesson 2009). In addition to diet and smoking, other sources of cadmium exposure for American Indian populations include living in the vicinity of industrial sites and mining areas (Moon et al. 1986; Schmitt et al. 2006), surface-dust in jewelry-making homes (Gonzales et al. 2004), and small scale motor vehicle repair (Yassin and Martonik 2004).

Methods

Study population

From 1989 to 1991, men and women 45-75 years of age from 13 American Indian communities were invited to participate in the SHS. In Arizona and Oklahoma every eligible person was invited, whereas in North/ South Dakota a cluster sampling technique was used (Lee et al. 1990). Among those invited, 62% agreed to participate and were evaluated at baseline (Stoddart et al. 2000), with a final sample of 4,545 participants. We excluded 580 participants due to insufficient urine available for metal analysis, 151 participants without information on smoking, 15 participants without body mass index (BMI) determinations, and 7 participants with missing information on alcohol consumption or education level, leaving 3,792 participants for these analyses. The SHS protocol was approved by institutional review boards, the Indian Health Service Institutional Review Board Review and by the participating communities. All participants provided oral and written informed consent.

Baseline data collection

Study visits were performed by trained and certified examiners following a standard protocol (Lee et al. 1990), and included a questionnaire (socio-demographic factors, smoking status, and medical history), a physical examination (height, weight, and blood pressure), and blood and urine collection. Participants having smoked at least 100 cigarettes in their lifetime and still smoking at baseline were considered current smokers. Past smoking was defined as noncurrent smokers who had smoked more than 100 cigarettes in their lifetime. Pack years were calculated as the amount of cigarette packs smoked per day times the number of years the person smoked. Current alcohol consumption was defined as any alcohol use in the past year. Former alcohol

consumption was defined as no use of any alcohol during the last year but previous use of more than 12 drinks of alcohol. Menopause was defined as the absence of a menstrual cycle for 12 or more months, a history of hysterectomy and oophorectomy, or a history of hysterectomy without oophorectomy and age 53 years or older. Hypertension was defined as mean systolic blood pressure ≥ 140 mm Hg, mean diastolic blood pressure ≥ 90 mmHg, or antihypertensive medication. Plasma creatinine was measured by an alkaline picrate rate method to estimate glomerular filtration rate (Levey et al. 2009), while urine creatinine was measured by an automated alkaline picrate methodology (Lee et al. 1990).

Urine cadmium determinations

The analytical methods used to measure urinary cadmium have been described in detail (Scherer and Barkemeyer 1983). In summary, we measured cadmium in spot urine samples using inductively coupled plasma mass spectrometry (Agilent 7700x ICPMS; Agilent Technologies, Waldbronn Germany). The limit of detection for urine cadmium was 0.015 μg/L and the inter-assay coefficient of variation was 8.7%. We imputed the urine cadmium concentration for one sample below the limit of detection as the limit of detection divided by √2.

Cancer mortality follow-up

Death certificates were obtained from the State Departments of Health. If the death certificate indicated that an autopsy had been performed, the medical examiner´s report was obtained (Lee et al. 2006). Primary and contributing causes of death were recorded according to the International Classification of Diseases, 9th Revision (ICD-9) (WHO 1977). In addition to total cancer, we evaluated the following specific cancers: esophagus and stomach (ICD-9 150-151), colon and rectum (ICD-9 153-154), liver and intrahepatic bile ducts (ICD-9 157), gallbladder

and extrahepatic bile ducts (ICD-9 156), bronchus and lung (ICD-9 162.2-162.9) (referred from now on as lung cancer), breast (ICD-9 174), prostate (ICD-9 185), kidney (ICD-9 189.0) and lymphatic and hematopoietic tissue (ICD-9 200-208). Finally we evaluated cancers with sufficient evidence of a causal association with tobacco smoking according to the IARC (IARC 2012) as a single group, including cancers of the lip, oral cavity and pharynx (ICD-9 140-149), esophagus (150), stomach (151), colon and rectum (153-154), liver (155), pancreas (157), larynx (161), trachea, bronchus and lung (162), cervix (180), bladder (188), kidney (189) and myeloid leukemia (205). The SHS uses tribal records, death certificates and direct annual contact with participants and their families to assess health outcomes and vital status over time. Follow-up for mortality was complete for 99.8% of the study population. We calculated follow-up from the date of baseline examination to the date of death or December 31st, 2008, whichever occurred first. The mean follow-up time among participants who did not develop cancer was 17.2 years.

Statistical methods

U-Cd concentrations were markedly right-skewed and natural log (ln) transformed for statistical analyses. To account for urine dilution in spot urine samples, we divided cadmium by urine creatinine. We conducted statistical analyses using Stata 11.2 (StataCorp, College Station, Texas).

We assessed the prospective association between creatinine-corrected cadmium concentrations and cancer mortality (overall and site-specific) using Cox proportional hazards models with age as the time scale and individual follow-up starting times (age at baseline examination) treated as staggered entries. This approach effectively adjusts for age. We visually evaluated the proportional hazards assumption based on Schoenfeld residuals, and did not observe any major

departures from proportionality (data not shown). To account for region, the non-parametric underlying baseline hazards were allowed to differ by study region using the strata command. We estimated associations with cadmium modeled as tertiles, with the lowest tertile as the reference level of exposure. For pancreas cancer, there was only 1 case in the first cadmium tertile and we combined the first and second tertiles. We also modeled ln-transformed cadmium as a continuous variable and derived hazard ratios comparing the 80^{th} vs the 20^{th} percentiles (i.e. interquintile range) of its distribution. Additionally, in a third set of models, we estimated associations with cadmium modeled as restricted cubic splines with knots at the 10^{th}, 50^{th} and 90^{th} percentiles.

All Cox proportional hazard models accounted for age and region (model 1). Model 2 was further adjusted for sex, and baseline BMI, smoking status, and cigarette pack-years. Model 2 also adjusted for baseline menopausal status (pre/post), hormone replacement therapy (current/past/never users) and parity (0/1-2/3-4/ $\geq$ 5) when breast cancer was the outcome of interest (Jain 2013; Sasco 2001; Vather et al. 2004), and for hypertension (no/yes) and glomerular filtration rate (continuous) when kidney cancer was the studied outcome (Brennan et al. 2008; Choi et al. 2005). To evaluate the consistency of our findings across subgroups, we performed separate exploratory models for total cancer mortality and smoking-related cancer mortality that included product interaction terms between ln-transformed cadmium and indicator variables for subgroups defined by age (< 55/55-64/$\geq$ 64 years), sex (male/female), post-menopausal status (pre/post), smoking status (never/ever/current) pack-years (0/1-4/5-19/$\geq$ 20) and urine arsenic concentrations (< 7/7-13/$\geq$ 13 μg/g) at baseline. We could not conduct interaction analyses for specific cancers due to the relatively small numbers of deaths.

We conducted several sensitivity analyses. First, to account for urine dilution we used two alternative strategies: adjusting for ln-transformed urine creatinine concentrations in µg/L instead of dividing by urine creatinine concentration, and adjusting for the overall mean specific gravity in the study population of 1.019 (McElroy et al. 2007). We restricted the latter analysis to participants without albuminuria or diabetes because specific gravity is inadequate to adjust for dilution if albumin or glucose is present in urine (Chadha et al. 2001; Voinescu et al. 2002). We also estimated associations without accounting for urine dilution. Second, to confirm that the findings were not affected by using age as the time scale, we re-evaluated the proportional hazards assumption for cadmium after fitting models using calendar time as the time scale and age as a covariate. Third, to account for competing risks by causes of death other than cancer, we estimated proportional hazard regression models according to the method of Fine and Gray. This method models the sub-hazard of the event of interest re-establishing the direct relationship between the sub-distribution of the hazard and the cumulative incidence function (Fine and Gray 1999). Fourth, to reduce the possibility that prevalent cancers at baseline could affect urine cadmium concentrations we repeated the analyses excluding participants who died of cancer during the first 2 or 5 years of follow-up. Fifth, to evaluate the stability of associations over time, we conducted separate analyses for the first and second decades of follow-up. Finally, because smoking is a major source of cadmium and adjustment for smoking might be insufficient to eliminate confounding by smoking, we repeated the analyses excluding current smokers. Findings from all sensitivity analyses were consistent with those reported.

To assess the role of cadmium as a possible mediator in the association between tobacco smoke and cancer mortality we calculated the proportion of additional cases of lung cancer due to

tobacco smoking that can be attributed to cadmium exposure, using the method proposed by Lange et al. (Lange and Hansen 2011), with bootstrap confidence intervals estimated as bias-corrected and accelerated percentile intervals. In brief, we first estimated the direct effect of smoking, as measured by pack-years, on cancer (direct pathway) using the Aalen additive hazard model. Then, we estimated the indirect effect using 2 models: 1) a linear regression with cadmium as the dependent variable and number of pack-years as the independent variable and 2) the Aalen additive hazard model for cadmium adjusted for pack-years. We estimated the proportion of lung cancer mortality associated with a 10 pack-year increase that can be attributed to urine cadmium as the ratio of the indirect effect to the total effect.

Results

During the follow-up period, 2,310 participants died, including 219 women and 155 men whose deaths were attributed to cancer. The most common cause of cancer deaths were lung (N = 34) and breast (N = 25) cancer in women, and lung (N = 43) and prostate (N = 16) cancer in men (Table 1). A total of 28 cancer deaths were unspecified (ICD-9: 194-199, 125 and 239). Older participants, those with lower education levels, participants living in North\South Dakota, current smokers and never drinkers at baseline had higher cancer mortality.

The median (IQR) concentration of cadmium at baseline was 1.02 (0.60-1.70) µg/L [0.93 (0.61-1.46) µg/g creatinine], with higher levels in participants from North\South Dakota than participants from Arizona or Oklahoma (Table 2). Lower creatinine-corrected urine cadmium levels were observed in men, participants under 55 years of age and participants with higher education. Current smokers and individuals with BMI values under 25 kg/m^2 showed the highest urine cadmium concentrations. Urine cadmium levels increased with increasing pack-years of

smoking in both former smokers (median cadmium levels among those smoking ≥ 20 ppy = 1.36 μg/g creatinine) and current smokers (median cadmium concentrations among those smoking ≥ 20 ppy = 1.57 μg/g creatinine).

After multivariable adjustment (Table 3), the hazard ratios (95%CI) for overall and for smoking-related cancer mortality comparing the 80th vs. 20th percentile of cadmium concentrations in urine were 1.30 (95%CI: 1.09, 1.55) and 1.56 (95%CI: 1.24, 1.96), respectively. The corresponding hazard ratios (95%CI) for cancers of the lung and pancreas were 2.27 (95%CI: 1.58, 3.27) and 2.40 (95%CI: 1.39, 4.17), respectively. After removing current smokers, the hazard ratios for overall, smoking-related, pancreatic and lung cancer mortality remained positive but weaker (Table 4). Cadmium was not significantly associated with other cancers, although the hazard ratios comparing the 80th vs. 20th percentile of cadmium concentrations were positive for liver cancer [1.64 (95%CI: 0.81, 3.13)] and lymphohematopoietic tumors [1.40 (95%CI:0.80, 2.43)].

When modeling the dose-response relationship using restricted cubic splines, we found increased risks with increasing urine cadmium concentrations for overall, smoking-related, lung and pancreatic cancer mortality, with no statistically significant departures from linearity (Figure 1). The associations for overall, smoking-related, pancreas and lung cancers were attenuated in models that did not account for urine dilution (Supplemental Material, Table S1).

In subgroup analyses, the fully-adjusted hazard ratios for all-cancer mortality and for smoking-related cancer mortality comparing the 80th vs. 20th percentiles of cadmium were consistent for all participants' subgroups evaluated, including smoking status, although these associations seemed stronger among current smokers (Figure 2).

Analyses investigating cadmium as a possible mediator of the association between tobacco smoke and lung cancer mortality suggested that the percentage of cancer deaths due to tobacco smoking that could be attributed to cadmium was 9.0% (95%CI: 2.8%, 21.8%), assuming no other mediators in the model.

Discussion

Low to moderate cadmium exposure, as measured in urine, was associated with mortality from overall, smoking-related, lung and pancreas cancer over almost 20 years of follow-up. The associations remained after adjustment for socio-demographic and behavioral factors, including smoking status and pack-years at baseline. As expected, the associations for overall, smoking-related, lung and pancreas cancer were attenuated when not accounting for urine dilution, since urine dilution is an important source of measurement error in this population with a high burden of uncontrolled diabetes (Lee et al. 1995). Our findings are consistent with previous cohort studies showing increased incidence and mortality for overall (Menke et al. 2009; Nawrot et al. 2006), lung (Adams et al. 2012; Nawrot et al. 2006; Verougstraete et al. 2003), and pancreas cancers (Adams et al. 2012) in association with cadmium exposure. Contrary to other studies, however, we found no significant positive association with prostate (Julin et al. 2012b; Kolonel and Winkelstein 1977; Lemen et al. 1976; Sharma-Wagner et al. 2000), breast (Cantor et al. 1995; Gallagher et al. 2010; Julin et al. 2012a) or kidney cancer (Il'yasova and Schwartz 2005), although we had limited power to identify associations due to the small numbers of deaths for these cancers.

Cadmium exposure induces lung and pancreas cancer in rodent models (Huff et al. 2007; Waalkes 2003). Proposed mechanisms for cadmium carcinogenicity include oxidative stress

(Bertin and Averbeck 2006; Hart et al. 1999; Joseph 2009; Patra et al. 2011), inhibition of DNA repair systems (Jin et al. 2003; McMurray and Tainer 2003; Potts et al. 2003), inhibition of apoptosis (Joseph 2009), epigenetic modifications affecting gene transcription (Achanzar et al. 2000; Bertin and Averbeck 2006), or endocrine disruption (Byrne et al. 2009). In human airway epithelial cells, cadmium has been shown to promote inflammation through cytokines (Cormet-Boyaka et al. 2012) and increased reactive oxygen species formation (Son et al. 2012). *In vitro*, chronic exposure of human pancreatic duct epithelial cells to cadmium resulted in malignant cell transformation with increased secretion of metalloproteinases, increased invasiveness, and colony formation (Qu et al. 2012).

Smoking, a cause of several cancers including lung and pancreas cancer (IARC 2012), is an important source of cadmium exposure (Satarug and Moore 2004). In our study, associations of cadmium with lung cancer and pancreas cancer remained significant after adjusting for smoking status and pack-years at baseline, suggesting that cadmium is an independent risk factor for these tumors, although we cannot discard residual confounding. Moreover, although weaker, the associations remained consistent after excluding participants who were current smokers at baseline. We also hypothesized that cadmium could act as a mediator of the association between smoking and lung cancer mortality, and estimated that cadmium exposure via smoking explained 9.0% of the excess lung cancer mortality due to tobacco smoking. Mediation analyses are limited by series of assumptions, including that there is no unmeasured confounding. Cadmium is only one of the many carcinogens present in tobacco smoke and we had one single cadmium measure, which could be affected by measurement error.

Women have higher cadmium internal dose compared to men at similar exposure levels, possibly related to their generally higher gastrointestinal absorption (Vahter et al. 2002). It is unclear, however if this higher cadmium internal dose is associated with worse health outcomes in women compared to men. In our study there were no significant differences in overall or smoking-related cancer mortality by sex, although associations were somewhat stronger in men. Data from the Swedish Mammography Cohort, a population-based prospective cohort study of 55,987 postmenopausal women followed during an average of 12.2 years, recently showed that dietary cadmium intake was positively associated with overall breast cancer risk (Julin et al. 2012a). Similarly, results from this same cohort suggested an increased risk of endometrial cancer with increasing cadmium intake (Akesson et al. 2008). In the US, a study based on data from both a case-control sample and from NHANES 1999-2008 found an increased risk of breast cancer in women with urine cadmium levels over 0.60 μg/creatinine (Gallagher et al. 2010). In our study we found no association with breast cancer mortality, similar to what was observed in NHANES III (Adams et al. 2012), although we were limited by the small number of breast cancer deaths (n = 25) and by the lack of information on incident cases. We could not evaluate the association between urine cadmium and endometrial cancer mortality as only two women died from this cancer.

Results from our study do not support an increased risk of prostate cancer mortality with increasing urine cadmium concentrations. Rather, we found a non-significant inverse association. In occupationally exposed men, some (Lemen et al. 1976; Sharma-Wagner et al. 2000; van der Gulden et al. 1995), although not all (Kazantzis et al. 1988; Pukkala et al. 2009), epidemiologic studies have shown a positive association between cadmium exposure and prostate cancer

incidence and mortality. Inconsistent results have also been reported in non-occupational studies evaluating the association between urine cadmium and prostate cancer incidence (Julin et al. 2012b; Lin et al 2013) or prostate cancer mortality (Adams et al. 2012; Li Q et al. 2011).

A systematic review suggested an increased risk of kidney cancer in cadmium-exposed workers (Il'yasova and Schwartz 2005), but evidence from general populations is lacking. Cadmium has also been proposed as a contributor to liver cancer (Satarug 2012), with supportive evidence from China (Campbell et al. 1990). Finally, there is some animal evidence that cadmium could induce tumors of the hematopoietic system (Waalkes and Rehm 1994), although there is no epidemiological evidence to support this relationship. Using data from the Strong Heart Study we found no association between urine cadmium and mortality from kidney cancers, and observed a positive but non-significant association with liver and lymphohematopoietic cancer mortality. The small number of deaths in each type of cancer, however, limited our ability to detect associations.

Our study has other limitations. First, we could not exclude participants with cancer at baseline. Analyses excluding cancer deaths during the first 2 and 5 years of follow-up, however, showed similar results (data not shown). Second, we relied on death certificates to identify the cause of death and had no confirmation from hospital records or a cancer registry. Third, we used a single spot urine sample to measure cadmium concentrations. Recent studies have also indicated that urine cadmium in populations exposed to low-moderate levels might not reflect chronic cadmium exposure (Akerstrom et al. 2013). Finally, we had limited statistical power for individual cancer subtypes and for conducting effect modification analyses.

Strengths of this study include the prospective design and the long follow-up, the low rate of losses to follow-up and the low limit of detection for urine cadmium (Lee et al. 1990; Scheer et al. 2012). Furthermore, this study provides information on cancer mortality in American Indians, an understudied population whose cancer experience and cancer determinants have not been well described. The high concentrations of U-Cd found in these communities [geometric mean: 0.70 μg/g creatinine in men, 1.14 μg/g creatinine in women] when compared to the adult US general population during the same time period [geometric mean: 0.28 μg/g creatinine in men, 0.40 μg/g creatinine in women] (Menke et al. 2009) suggest that cadmium exposure may be an important environmental risk factor for cancer development in American Indians.

Conclusions

Our study contributes additional evidence in support of low-moderate cadmium exposure as a cancer risk factor, including total, lung, and pancreas cancer. The implementation of population-based preventive measures to decrease cadmium exposure, including tobacco control measures (Tellez-Plaza et al. 2012), reduction of dust in homes (Hogervorst et al. 2007), and decrease of the transfer of cadmium from soil to plants used for human consumption, for instance by maintaining agricultural soils pH close to neutral (Nawrot et al. 2010), could contribute to reducing the burden of cancer.

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Table 1. Baseline characteristics of study participants overall and by cancer mortality status.

Variable	Overall (N = 3,792)	Cancer death (N = 375)	Others (N = 3,417)	p-value[a]
Age, years	56.2 ± 0.13	60.2 ± 0.42	55.8 ± 0.14	< 0.001
Men, N (%)	1538 (40.6)	155 (41.3)	1383 (40.5)	0.72
Post-menopausal women[b], N (%)	1733 (76.9)	192 (86.8)	1541 (75.8)	< 0.001
Arizona, N (%)	1268 (33.5)	108 (28.8)	1160 (33.9)	0.05
Oklahoma, N (%)	1252 (33.0)	121 (32.3)	1131 (33.1)	0.77
Dakota, N (%)	1272 (33.5)	146 (38.9)	1126 (32.9)	0.02
< High school, N (%)	1799 (47.4)	202 (53.9)	1597 (46.7)	0.01
Current smoking, N (%)	1296 (34.1)	161 (42.9)	1135 (33.2)	< 0.001
Former smoking, N (%)	1212 (32.0)	113 (30.1)	1099 (32.2)	0.44
Cigarette pack-years	16.3 ± 0.41	22.7 ± 1.66	15.5 ± 0.41	< 0.001
Never drinking, N (%)	621 (16.4)	75 (20.0)	546 (16.0)	0.01
BMI, kg/m^2	30.9 ± 0.10	30.4 ± 0.34	30.9 ± 0.11	0.11

Data in the table are numbers and percentages for categorical variables or means ± SD for continuous variables.

[a]P-values for the null hypothesis that there are no differences in the distribution of the main variables by cancer status are based on the chi-square test for qualitative variables and analysis of the variance for quantitative variables. [b] Subsample of women (N = 2,254).

Table 2. Median (IQR) urine cadmium concentrations by participant characteristics at baseline.

Variable	Category	N	Median (IQR) (µg/g creatinine)	p-value[a]	Median (IQR) (µg/l)	p-value[a]
Overall	Total	3792	0.93 (0.61-1.46)		1.02 (0.60-1.70)	
Age	< 55	1883	0.88 (0.57-1.35)	< 0.001	1.01 (0.58-1.69)	0.26
	55-64	1166	1.00 (0.65-1.56)		1.06 (0.65-1.73)	
	≥ 64	743	0.98 (0.63-1.53)		0.98 (0.56-1.66)	
Sex	Male	1538	0.71 (0.46-1.08)	< 0.001	0.95 (0.56-1.59)	0.003
	Female	2254	1.11 (0.74-1.71)		1.06 (0.63-1.78)	
Post-menopausal women	Yes	521	1.03 (0.70-1.51)	0.001	1.17 (0.62-1.87)	< 0.001
	No	1733	1.13 (0.75-1.74)		1.03 (0.63-1.74)	
Center	Arizona	1268	0.82 (0.55-1.22)	< 0.001	0.84 (0.51-1.36)	< 0.001
	Oklahoma	1252	0.87 (0.57-1.35)		0.96 (0.58-1.62)	
	Dakota	1272	1.13 (0.75-1.80)		1.30 (0.76-2.10)	
Education level	< High school	834	1.01 (0.66-1.57)	< 0.001	1.00 (0.60-1.68)	< 0.001
	High school	965	1.01 (0.65-1.59)		1.02 (0.61-1.78)	
	> High school	1993	0.88 (0.57-1.34)		1.02 (0.60-1.67)	
Smoking status	Never	1284	0.88 (0.57-1.36)	< 0.001	0.86 (0.53-1.40)	< 0.001
	Former	1212	0.79 (0.53-1.22)		0.90 (0.55-1.49)	
	Current	1296	1.14 (0.74-1.73)		1.36 (0.80-2.18)	
Cigarette pack-years	0	1284	0.88 (0.57-1.36)	< 0.001	0.86 (0.53-1.40)	< 0.001
	1-4	931	0.84 (0.54-1.29)		0.92 (0.56-1.56)	
	5-19	748	0.93 (0.62-1.44)		1.18 (0.70-1.88)	
	> = 20	829	1.14 (0.76-1.72)		1.33 (0.77-2.19)	
Alcohol	Never	621	1.03 (0.67-1.59)	< 0.001	0.96 (0.56-1.66)	0.01
	Former	1583	0.91 (0.60-1.46)		0.96 (0.58-1.64)	
	Current	1588	0.91 (0.59-1.39)		1.09 (0.64-1.78)	
BMI, kg/m^2	< 25	591	1.17 (0.75-1.84)	< 0.001	1.19 (0.65-2.05)	< 0.001
	25-30	1276	0.96 (0.61-1.50)		1.02 (0.61-1.69)	
	> = 30	1925	0.86 (0.57-1.30)		0.97 (0.58-1.61)	

[a]P-value from Kruskall-Wallis exact test.

Table 3. Hazard ratios (95%CI) for cancer mortality by urine cadmium levels (μg/g creatinine).

Outcome	Cd ≤ 0.70	Cd 0.71-1.22	Cd ≥ 1.23	80th vs. 20th percentiles[a]	p-trend[b]
Total cancer (ICD-9 140 to 208)					
Cases / Total	77/1269	142/1266	156/1257	375/3792	
Model 1	1 (Referent)	1.80 (1.36, 2.38)	1.94 (1.47, 2.57)	1.36 (1.16, 1.59)	<0.001
Model 2	1 (Referent)	1.76 (1.32, 2.35)	1.85 (1.36, 2.51)	1.30 (1.09, 1.55)	<0.001
Smoking related cancers[c] (ICD-9 140-149, 150-151, 153-155, 157, 161, 162, 180, 188-189, 205)					
Cases / Total	34/1269	72/1266	104/1257	210/3792	
Model 1	1 (Referent)	2.04 (1.36, 3.07)	2.81 (1.90, 4.16)	1.56 (1.28, 1.91)	<0.001
Model 2	1 (Referent)	2.04 (1.34, 3.11)	2.80 (1.82, 4.31)	1.56 (1.24, 1.96)	<0.001
Esophagus and stomach cancer (ICD-9 150-151)					
Cases / Total	11/1269	6/1266	7/1257	24/3792	
Model 1	1 (Referent)	0.55 (0.20, 1.49)	0.68 (0.26, 1.79)	0.63 (0.33, 1.20)	0.16
Model 2	1 (Referent)	0.60 (0.21, 1.68)	0.76 (0.26, 2.23)	0.68 (0.34, 1.38)	0.29
Colon and rectal cancer (ICD-9 153-154)					
Cases / Total	6/1269	14/1266	12/1257	32/3792	
Model 1	1 (Referent)	2.27 (0.87, 5.93)	1.76 (0.65, 4.75)	1.06 (0.60, 1.86)	0.84
Model 2	1 (Referent)	2.23 (0.82, 6.02)	1.74 (0.60, 5.11)	0.98 (0.51, 1.88)	0.96
Liver and intrahepatic bile ducts (ICD-9 155)					
Cases / Total	4/1269	7/1266	10/1257	21/3792	
Model 1	1 (Referent)	1.79 (0.52, 6.14)	2.83 (0.87, 9.14)	1.51 (0.81, 2.81)	0.20
Model 2	1 (Referent)	2.11 (0.59, 7.55)	3.67 (1.01, 13.32)	1.64 (0.81, 3.13)	0.14
Gallblader and extrahepatic bile ducts (ICD-9 156)					
Cases / Total	3/1269	5/1266	3/1257	11/3792	
Model 1	1 (Referent)	1.56 (0.37, 6.57)	0.94 (0.19 ,4.77)	1.13 (0.44, 2.86)	0.80
Model 2	1 (Referent)	1.28 (0.29, 5.67)	0.66 (0.11, 3.90)	0.89 (0.31, 2.54)	0.82
Pancreas (ICD-9 157)[d]					
Cases / Total	12/1269	-	12/1257	24/3792	
Model 1	1 (Referent)	-	2.00 (0.89, 4.52)	2.00 (1.19, 3.36)	0.009
Model 2	1 (Referent)	-	2.47 (1.01, 6.03)	2.40 (1.39, 4.17)	0.002

Outcome	Cd ≤ 0.70	Cd 0.71-1.22	Cd ≥ 1.23	80th vs. 20th percentiles[a]	p-trend[b]
Bronchus and lung (ICD-9 162)					
Cases / Total	4/1269	21/1266	52/1257	77/3792	
Model 1	1 (Referent)	4.85 (1.66, 14.1)	10.2 (3.67, 28.4)	2.33 (1.76, 3.09)	< 0.001
Model 2	1 (Referent)	3.39 (1.14, 10.1)	6.65 (2.29, 19.3)	2.27 (1.58, 3.27)	< 0.001
Breast (ICD-9 174)					
Cases / Total	6/504	12/786	7/964	25/ 2254	
Model 1	1 (Referent)	1.29 (0.48, 3.47)	0.60 (0.20, 1.83)	1.01 (0.51, 1.98)	0.15
Model 2	1 (Referent)	1.34 (1.14, 10.1)	0.58 (0.18, 1.83)	1.02 (0.50, 2.07)	0.96
Prostate (ICD-9 185)					
Cases / Total	4/765	8/480	4/293	16/1538	
Model 1	1 (Referent)	1.80 (0.54, 6.00)	0.85 (0.2, 3.48)	0.70 (0.30, 1.62)	0.41
Model 2	1 (Referent)	1.37 (0.40, 4.66)	0.48 (0.11, 2.08)	0.42 (0.16, 1.08)	0.07
Kidney (ICD-9 189)					
Cases / Total	8/1269	11/1266	6/1257	26/3792	
Model 1	1 (Referent)	1.40 (0.56, 3.50)	0.82 (0.28, 2.42)	0.83 (0.44, 1.56)	0.64
Model 2	1 (Referent)	1.92 (0.73, 5.01)	1.39 (0.43, 4.58)	1.15 (0.58, 2.31)	0.61
Lymphohematopoietic tissue (ICD-9 200–208)					
Cases / Total	6/1269	17/1266	14/1257	37/3792	
Model 1	1 (Referent)	2.96 (1.16, 7.52)	2.73 (1.04, 7.20)	1.45 (0.87, 2.40)	0.15
Model 2	1 (Referent)	2.94 (1.12, 7.70)	2.79 (0.99, 7.90)	1.40 (0.80,2.43)	0.24

Model 1: Adjusted for sex and age

Model 2: Adjusted for sex, age, smoking status (never, former, current), pack-years (continuous) and BMI (< 25, 25-30, ≥ 30 kg/m^2). Model 2 for breast cancer was further adjusted for menopausal status (pre, post), parity (0, 1-2, 3-4, ≥ 5) and hormonal replacement therapy (current, past, never use). Model 2 for kidney cancer was further adjusted for estimated glomerular filtration rate (continuous) and hypertension status (yes,no).

[a] Models comparing the 80th vs. 20th percentiles of urine cadmium and associated p-trend were obtained from Cox proportional hazards models with ln-transformed cadmium as a continuous variable. These models allow us compute the expected association comparing cadmium levels at the the 80th percentile (1.62 µg/g creatinine) to those on the 20th percentile (0.55 µg/g creatinine) (i.e and interquintile range). [b] p-trend from the Log Likelihood Ratio test calculated modeling ln-cadmium as continuous. [c] Smoking related cancers: Lip, oral cavity and pharynx (140-149), esophagus (150), stomach (151), colon and rectum (153-154), liver (155), pancreas (157), larynx (161), trachea, bronchus and lung (162), cervix (180), bladder (188), kidney (189), myeloid leukemia (205). [d] Tertiles 1 and 2 were combined in one single group because there was only one case in the first tertile.

Table 4. Hazard ratios (95%CI) for cancer mortality comparing the 80th vs. 20th percentiles of urine cadmium concentrations in all participants and in non-current smokers (never and former smokers).

	All participants	**Never and former smokers**
Total cancer		
Cases/Total	375/3792	214/2496
Model 2	1.30 (1.09, 1.55)	1.17 (0.93, 1.48)
Smoking related cancers		
Cases/Total	210/3792	107/2496
Model 2	1.56 (1.24, 1.96)	1.37 (1.00, 1.87)
Pancreas		
Cases/Total	24/3792	15/2496
Model 2	2.41 (1.39, 4.17)	2.22 (1.12, 4.40)
Bronchus/lung		
Cases/Total	77/3792	17/2496
Model 2	2.27 (1.58, 3.27)	2.06 (1.15, 3.70)

Figure Legends

Figure 1. Hazard ratios (95% confidence intervals) for overall, smoking-related, lung and pancreas cancer mortality based on restricted cubic splines for ln-transformed urine cadmium concentrations with knots at the 10^{th} (0.4 µg/g creatinine), 50^{th} (0.93 µg/g creatinine) and 90^{th} (2.15 µg/g creatinine) percentiles. The reference value is set at the 10th percentile of the cadmium distribution. Hazard ratios are adjusted for sex, age, smoking status, pack-years and BMI. Lines represent the HR (thick line) and 95%CIs (dotted lines), and vertical bars represent the histogram of urine cadmium distribution. The p-value for the linear and non-linear components of the dose-response relationship were, respectively, 0.03 and 0.26 for overall cancer, 0.02 and 0.25 for smoking-related cancers, 0.02 and 0.09 for pancreas cancer and 0.01 and 0.10 for lung cancer. The p-value for the non-linear component was estimated using the Wald test

Figure 2. Hazard ratios (95% confidence intervals) for overall and smoking-related cancer mortality comparing the 80^{th} vs. 20^{th} percentiles of cadmium (µg/g creatinine) by participant characteristics at baseline.

Figure 1.

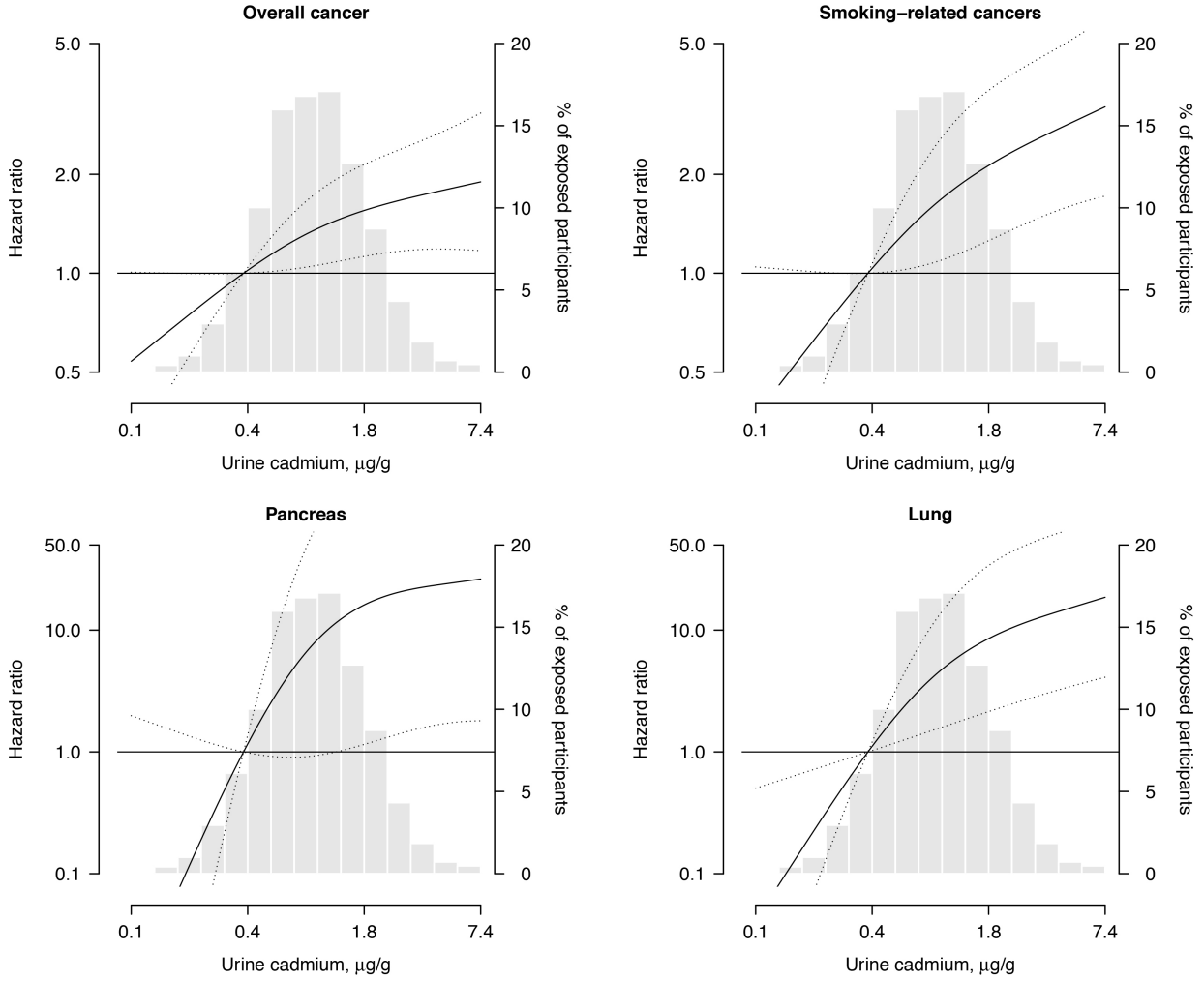
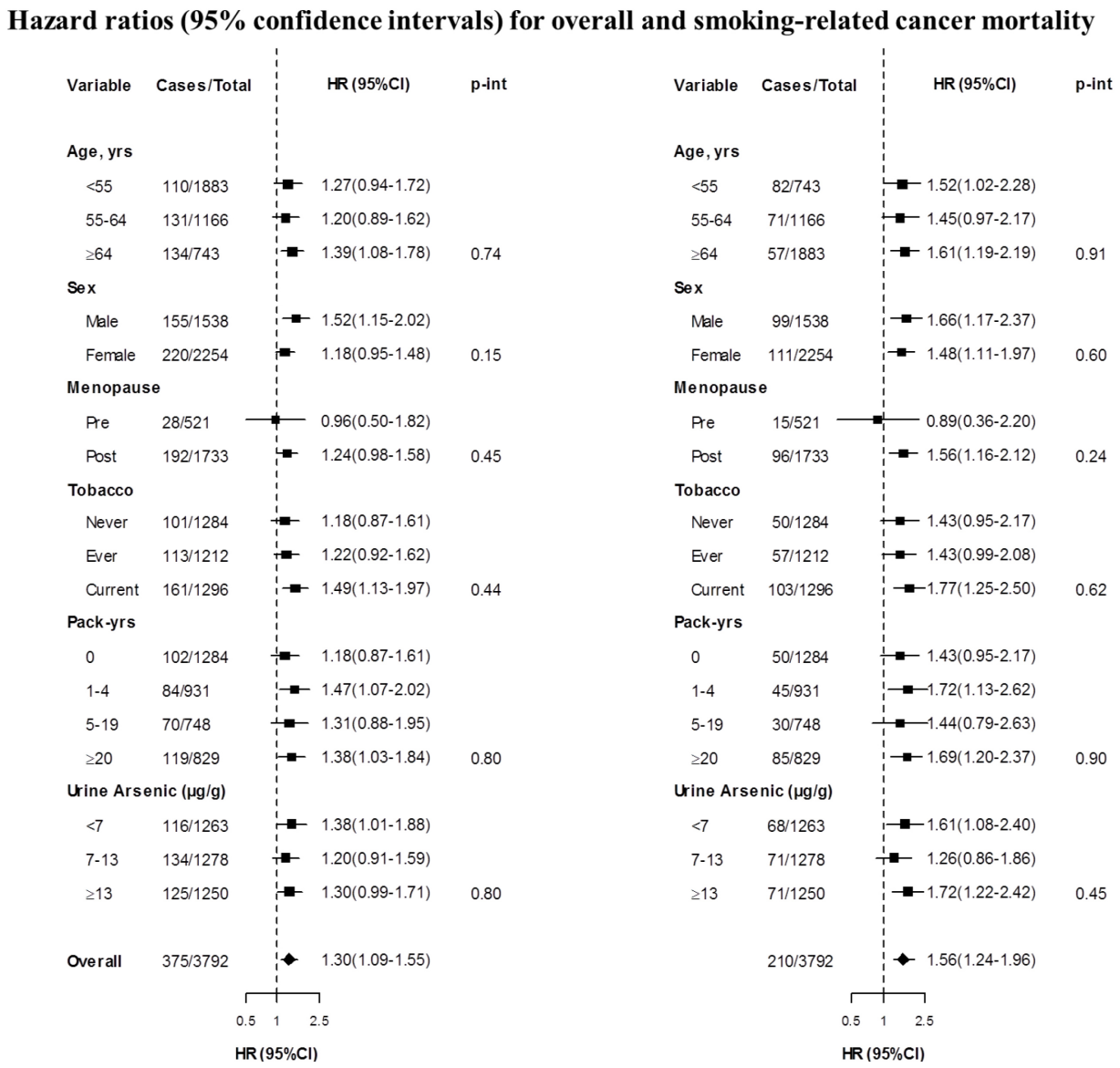

Overall cancer
Smoking−related cancers
Pancreas
Lung
Hazard ratio
% of exposed participants
Urine cadmium, µg/g
0.1
0.4
1.8
7.4
0.5
1.0
2.0
5.0
10.0
50.0
0
5
10
15
20

Figure 2.


Hazard ratios (95% confidence intervals) for overall and smoking-related cancer mortality
Variable
Cases/Total
HR (95%CI)
p-int
Age, yrs
<55 110/1883 1.27(0.94-1.72)
55-64 131/1166 1.20(0.89-1.62)
≥64 134/743 1.39(1.08-1.78) 0.74
Sex
Male 155/1538 1.52(1.15-2.02)
Female 220/2254 1.18(0.95-1.48) 0.15
Menopause
Pre 28/521 0.96(0.50-1.82)
Post 192/1733 1.24(0.98-1.58) 0.45
Tobacco
Never 101/1284 1.18(0.87-1.61)
Ever 113/1212 1.22(0.92-1.62)
Current 161/1296 1.49(1.13-1.97) 0.44
Pack-yrs
0 102/1284 1.18(0.87-1.61)
1-4 84/931 1.47(1.07-2.02)
5-19 70/748 1.31(0.88-1.95)
≥20 119/829 1.38(1.03-1.84) 0.80
Urine Arsenic (µg/g)
<7 116/1263 1.38(1.01-1.88)
7-13 134/1278 1.20(0.91-1.59)
≥13 125/1250 1.30(0.99-1.71) 0.80
Overall 375/3792 1.30(1.09-1.55)
0.5 1 2.5
HR (95%CI)
Variable
Cases/Total
HR (95%CI)
p-int
Age, yrs
<55 82/743 1.52(1.02-2.28)
55-64 71/1166 1.45(0.97-2.17)
≥64 57/1883 1.61(1.19-2.19) 0.91
Sex
Male 99/1538 1.66(1.17-2.37)
Female 111/2254 1.48(1.11-1.97) 0.60
Menopause
Pre 15/521 0.89(0.36-2.20)
Post 96/1733 1.56(1.16-2.12) 0.24
Tobacco
Never 50/1284 1.43(0.95-2.17)
Ever 57/1212 1.43(0.99-2.08)
Current 103/1296 1.77(1.25-2.50) 0.62
Pack-yrs
0 50/1284 1.43(0.95-2.17)
1-4 45/931 1.72(1.13-2.62)
5-19 30/748 1.44(0.79-2.63)
≥20 85/829 1.69(1.20-2.37) 0.90
Urine Arsenic (µg/g)
<7 68/1263 1.61(1.08-2.40)
7-13 71/1278 1.26(0.86-1.86)
≥13 71/1250 1.72(1.22-2.42) 0.45
210/3792 1.56(1.24-1.96)
0.5 1 2.5
HR (95%CI)